

REMARKS

Applicants acknowledge with appreciation the cordial personal interview accorded the lead inventor, Dr. Antonio Nanci, and his counsel by Examiners Celine Qian and Ann Falk on January 27, 2004 at which the nature of the invention and the distinctions over the prior art were discussed in detail. The following remarks are respectfully submitted to reflect the discussion which took place at the interview. Also attached hereto as an exhibit are copies of the slides (with minor errors of spelling and grammar corrected) from a Powerpoint presentation shown to the Examiners at the interview.

Original claims 1-14 have been canceled and replaced by new claims 15-34 which are respectfully submitted to more particularly point out and distinctly claim that which applicants regard as their invention and to be in better form for examination by the U.S. Patent and Trademark Office. Support for the new claims is found, *inter alia*, in original claims 1-12.

Regarding the requirement for restriction, the claims of groups VII and VII have been canceled without prejudice to, or disclaimer of applicants' rights to prosecute the subject matter thereof in an appropriate divisional application. The rejoinder of Groups I and II is acknowledged with appreciation. Reconsideration of the restriction of the claims of Groups III, IV and V is respectfully requested. All the claims of the application share the special technical feature of the claimed *in vivo* animal model. This model is recited and required in every claim, and this common claim feature alone is sufficient show that unity of invention is present. The fact that some of the claims may also recite additional novel features does not change this. (See MPEP, Page AI-69, Example 12). Accordingly, reconsideration and withdrawal of the restriction as to the claims of Groups III, IV and V are respectfully requested.

The comments regarding the Oath or Declaration are acknowledged, however, it is believed that there is no defect in the originally submitted Declaration. The submitted Declaration properly identifies the inventors and

indicates the citizenship of each of them. Residence information for each of the inventors was properly given on an Application Data Sheet submitted June 18, 2001 as provided in 37 C.F.R. §1.76 and §1.63(c) at the time U.S. national stage entry was commenced. Accordingly, the Declaration is proper, and reconsideration and withdrawal of the objection are requested.

An Abstract of the Disclosure based on the abstract of the published PCT application is submitted herewith.

Any reasons which may have existed for the rejection of claims under 35 U.S.C. §112, first paragraph, for alleged lack of enablement are believed overcome by the amendments to the claims which limit the invention to local administration of the test substance through the window of the model as suggested in the Office Action. Evaluation of histological and histomorphometric parameters is clearly within the skill of the art as evidenced by the quotations from Erikisen et al, Bone Histomorphometry p. 74, Raven Press (1994) on page 4 of the attached Powerpoint presentation, as well as the attached Mocetti et al. article from the Journal of Histochemistry and Cytochemistry 48(8):1059-77 (2000). Accordingly, reconsideration and withdrawal of the §112 enablement rejection are respectfully requested.

The indefiniteness rejection of claim 7 (replaced by new claim 23) is respectfully traversed. "Growth factors" are a known class of protein to persons skilled in the art, and persons skilled in the art are accustomed to use of this term to identify this class of proteins. Thus, the term "growth factor" is submitted to have a readily ascertainable meaning to persons of ordinary skill in this art, and its use in the claim does not render the claim indefinite. Reconsideration and withdrawal of the indefiniteness rejection are therefore respectfully requested.

The rejection of claims as obvious under 35 U.S.C. §103(a) over Ouhayoun et al., Journal of Materials Science: Materials in Medicine 3:222-28 (1992) is respectfully traversed. Before discussing in detail the reasons why this

document fails to render the claimed invention obvious, a brief explanation of the nature of the invention is in order.

The presently claimed invention is a test model useful to evaluate the effects of test substances on cell and tissue activities, and particularly on developing odontological tissues. The model comprises a mandible of a rodent or other mammal with continuously growing incisors in which a window is surgically formed for local administration of the test substance in the immediate vicinity of the continuously erupting incisor. Unlike the teeth of man and most other mammals, which emerge in a mature state and do not grow thereafter, the incisors of rodents and a few other gnawing animals grow continuously to replace the emerged end which is constantly being worn away by the gnawing activity of the animal. Because the continuously erupting incisor is accessible at all locations along its length and represents all stages of tissue development from stem cell division and differentiation at the apical end to mature tooth at the emerging end, the test model of the invention makes it possible to evaluate the effect of the substance at all stages of tissue development. Indeed, multiple generations of cells can be studied and not just a single generation. Moreover, because the incisor is surrounded by a compartment, it is possible to locally administer the test substance in the immediate vicinity of the continuously erupting incisor without damaging the incisor or interrupting its ongoing development, thereby making it possible to study anabolic and/or catabolic activities and not just the repair of damaged tissue. In addition, because rodents and like animals with continuously erupting incisors have two separate hemimandibles, the other hemimandible of the test animal can be used as an independent control eliminating the possibility of errors due to differences between experimental animals and control animals.

The cited Ouhayoun et al. article describes a distinctly different system. Ouhayoun et al. disclose a pig mandible model for studying the effects of bone augmentation materials. Ouhayoun et al. introduce test materials into bone

defects formed at the roots of mature teeth and then monitor the healing of those defects. Because the teeth are mature teeth, there is no continuous growth and no possibility of studying the effects of the substances at different stages of tissue development. Moreover, because the test substance is introduced by damaging tissue to create a defect, only the healing or repair of a defect can be studied, and not the effects of the test substance on ongoing tissue development. In addition, because a swine has only one mandible, there is no possibility of using the same animal both as a test subject and as a control; a different animal must be used as a control thereby introducing the possibility that differences in observed results may be due to differences between the animals and not to the test substance. Not only is the test model of Ouhayoun et al. distinctly different from the presently claimed invention, but Ouhayoun et al. neither contains the slightest suggestion of the modifications needed to arrive at the presently claimed invention nor evidences even the slightest awareness or appreciation of the significant advantages achieved with the test model of the invention. Thus, Ouhayoun et al. fails to render the presently claimed invention obvious.

Nevertheless, the Office Action of August 26, 2003 asserts that it would be obvious to a person of ordinary skill in the art to adapt the Ouhayoun et al. swine model to other animals, including rodents. However, even assuming *arguendo* that this were true, the result would not be the same as the presently claimed invention. This is because any attempt to apply the teachings of Ouhayoun et al. to rodents would necessarily seek to apply them in an analogous manner, and the analogous location in a rodent is not the location targeted by the present invention. As can be clearly seen in the drawing on page 2 and the photographs on page 4 of the attached Powerpoint presentation, in addition to their continuously erupting incisors, rodents also have mature teeth (molars) which do not grow continuously. Since these rodent molars are most analogous to the mature swine teeth of the Ouhayoun et al. model, they would be the most likely target for adaptation of the Ouhayoun et al. model to rodents. But the

result of such an analogous adaptation would fail to achieve the significant advantages of the present invention and would merely preserve all of the disadvantages of the Ouhayoun et al. swine model. It was only the present applicants who recognized the advantages of targeting the continuously erupting incisors of rodents and like animals, rather than mature teeth as in the Ouhayoun et al. swine model, in order to be able to evaluate the effects of test substances on various developmental stages of tissues which are present in such continuously erupting teeth. This pivotal insight was not rendered obvious by Ouhayoun et al. Accordingly, reconsideration and withdrawal of the obviousness rejection are respectfully requested.

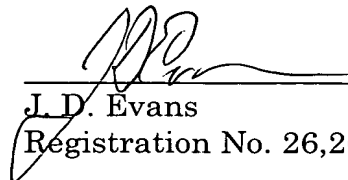
In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned at (202) 624,2845 would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #02904950108).

Respectfully submitted,

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